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Brief Communications

Outcomes of Pregnancy During Immunotherapy Treatment for Cancer: Analysis of Clinical Trials Sponsored by the National Cancer Institute

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Despite expanding indications for immunotherapeutic agents, there is limited understanding about their clinical effects on pregnancy outcomes. Generally, pregnant patients with cancer are excluded from clinical trials, and inadvertent pregnancies on trial result in patients being taken off because of concerns for fetal toxicity. To answer this question of pregnancy outcomes on immunotherapy-based trials, we performed a retrospective analysis of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)-Adverse Event Reporting System for unexpected pregnancies during NCI-CTEP–sponsored immunotherapy clinical trials between 2011 and 2020. We identified nine female patients who had unexpected pregnancies, of whom seven chose to take their pregnancies to term. All seven pregnancies resulted in vaginal births of apparently normal infants. This is the first report of pregnancy outcomes in multiple female patients exposed to immunotherapy. Our data suggest the need for further research to better evaluate and define contraception recommendations during immunotherapy treatment for cancer. ***The Oncologist*** 2021;26:e1883–e1886

Introduction

The last several decades have seen a gradual increase in the mean age of childbearing in the U.S. [1]. As a result, more women who are yet to complete their families are at risk of dealing with a cancer diagnosis and pregnancy at the same time [2]. Immune checkpoint inhibitors (ICIs) and other immunotherapies are effective in many different cancers, but little is known about the effect of these potent immune modulators on pregnancy outcomes and safety in humans [2].

The most important ICIs currently in clinical use inhibit the immune checkpoint programmed cell death-1 (PD-1), its ligand programmed cell death ligand-1 (PD-L1), or cytotoxic T-cell antigen-4 (CTLA-4). In addition to tumor immunology, these axes play an important role in maintaining maternal immune tolerance toward the developing fetus. Their stimulation causes proliferation of regulatory T cells (Tregs), which downregulate antigen-specific T-cell activity at the maternal-fetal interface and allow the genetically distinct fetus and mother to coexist [3, 4]. In animal models, inhibiting these immune checkpoints caused an increased incidence of spontaneous abortions in rodents and stillbirths in nonhuman primates, although surviving infants had no apparent malformations noted [4]. Most clinical trials exclude pregnant women and require patients of reproductive potential to use two contraceptive methods while receiving ICIs and up to 6 months after the last dose. Similar recommendations are used when treating pregnant patients in clinical practice. However, there is a lack of human data evaluating the effects of this class of immunotherapeutic agents and cancer vaccines on pregnancy and the developing fetus.

Materials and Methods

To address this knowledge gap, we performed a retrospective analysis of the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program-Adverse Event Reporting System (CTEP-AERS), collecting reports of unexpected

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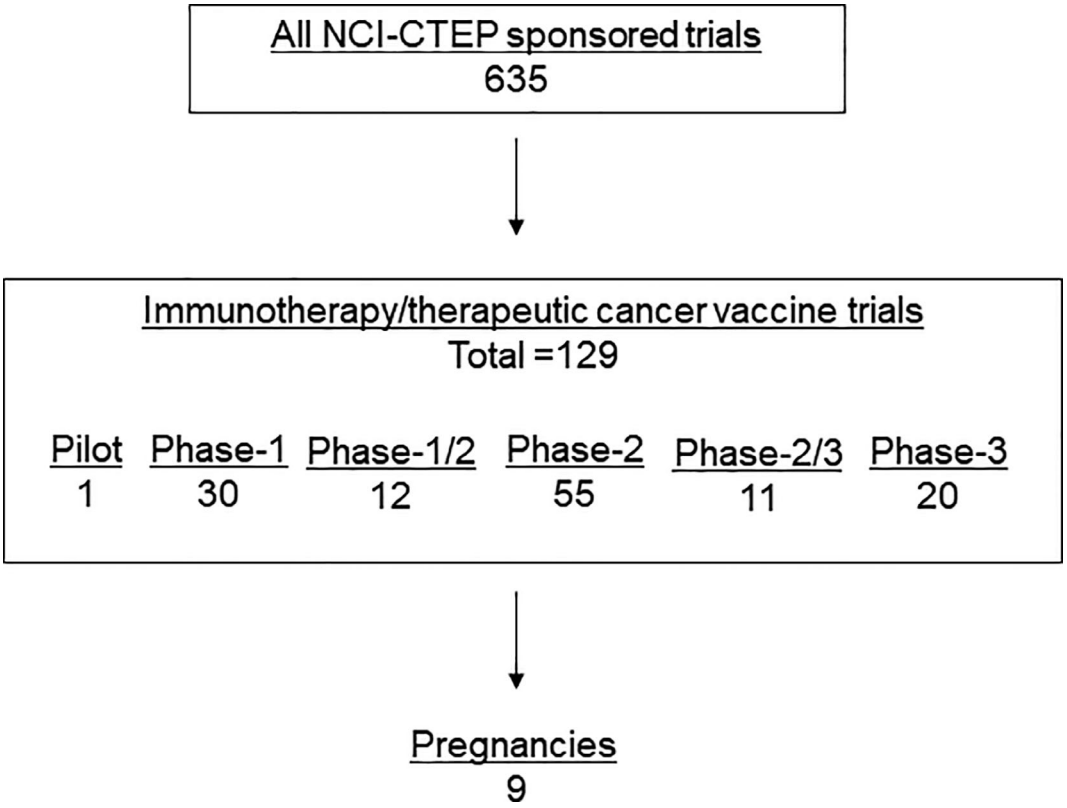

Figure 1. Identification of female patients who became pregnant on National Cancer Institute's Cancer Therapy Evaluation Program sponsored immunotherapy or therapeutic cancer vaccine trials that were open to enrollment any time between January 1, 2011, and August 25, 2020

pregnancies in patients on NCI sponsored clinical trials between January 1, 2011, and August 25, 2020. We further identified patients who became pregnant while receiving immunotherapy agents (ICIs or cancer vaccines). All the trials from which data was collected were approved by the respective institutional review boards.

Results

NCI/CTEP had a total of 635 trials open to enrollment any time between January 1, 2011, and August 25, 2020. Of these, 129 were immunotherapy or therapeutic cancer vaccine trials: 1 pilot, 30 phase I, 12 phase I/II, 55 phase II, 11 phase II/III, and 20 phase III studies. From these trials, we identified nine female patients with unexpected pregnancies while on treatment with, or soon after (during the trial follow-up period) receiving, immunotherapy (Fig. 1).

The median age at pregnancy was 27 years (range, 21–36), with a median length of treatment of 24 weeks (range, 3.1–61). Seven of nine patients had resected melanoma treated with adjuvant immunotherapy, and two patients had other cancers treated for advanced disease. Patients received PD-1/PD-L1 inhibitors (4 patients), CTLA-4 inhibitors (2 patients), CTLA-4 + PD-1 inhibitor (2 patients), or a cancer vaccine (1 patient).

Once pregnancy was discovered, treatment was stopped on all seven patients still on trial treatment, whereas the other two patients had already completed treatment and were in the trial follow-up period. Seven of nine women chose to carry their pregnancies to term (3 PD-1/PDL-1, 2 CTLA-4, 1 CTLA-4 + PD-1, 1 cancer vaccine), and two women chose elective first-trimester terminations. Six of the seven women carrying their pregnancies had full-term vaginal deliveries, whereas one developed preeclampsia resulting in a premature live vaginal birth. At a median postpartum follow-up of 4 weeks (range, 0.9–56. weeks), all seven infants were reported to be normal (per NCI/CTEP pregnancy report form terminology; Table 1).

Discussion

These data are the first reported analysis of pregnancy outcomes in multiple female patients exposed to immunotherapy to treat cancer. Our study is also the largest database evaluation of ICI-based trials sponsored by the NCI to identify female patients who conceived while on active treatment. Importantly, in this study, all patients treated with either ICIs or a cancer vaccine who chose to carry their pregnancies to term gave birth to apparently normal infants. The data currently available on pregnancies during immunotherapy are restricted to case reports of female patients diagnosed with cancer during pregnancy and treated with checkpoint blockade [5, 6]. One of these is a report of a female patient with melanoma diagnosed during pregnancy who received combination anti-PD-1/anti-CTLA-4 therapy in the first trimester, which resulted in the birth of a live infant with no apparent complication [6]. Of note, there was regression of some of the melanoma lesions, and the patient developed

Table 1. Pregnancy outcomes of female patients receiving immunotherapy

Patient number	Age	Primary tumor	Resected or advanced	Agent	Total length of treatment, wk	Estimated timing of conception	Gestational age at time of pregnancy diagnosis, wk	Outcome of pregnancy	Delivery method	Pregnancy complications	Health of infant	Length of follow-up after delivery or termination, wk
1	21	Melanoma	Resected	Vaccine	12.1	On trial	2.0	Live birth	Vaginal	None	Normal	56.3
2[a]	24	Melanoma	Resected	Ipilimumab	60.1	~9 wk after last dose	14.4	Live birth	Vaginal	None	Normal	4.0
3	36	Melanoma	Resected	Pembrolizumab	24.0	On trial	1.1	Live birth	Vaginal	None	Normal	1.3
4[b]	25	Sarcoma	Advanced	Atezolizumab	57.3	On trial	5.3	Live birth	Vaginal	Preeclampsia, Prematurity	Normal	0.9
5[a]	30	Melanoma	Resected	Pembrolizumab	51.4	~ 11 wk after last dose	7.3	Live birth	Vaginal	None	Normal	13.6
6	31	Melanoma	Resected	Ipilimumab	23.9	On trial	2.7	Live birth	Vaginal	None	Normal	6.1
7	21	Eccrine carcinoma	Advanced	Ipilimumab + nivolumab	30.0	On trial	6.6	Live birth	Vaginal	None	Normal	2.3
8	25	Melanoma	Resected	Pembrolizumab	3.1	On trial	Not known	Elective termination	NA	NA	NA	22.7
9	33	Melanoma	Resected	Ipilimumab + nivolumab	61.0	On trial	3.4	Elective termination	NA	NA	NA	2.0

Severe hypertension resolved after delivery. The newborn was admitted to the neonatal intensive care unit and was reported to be normal at last follow-up.

[a]Patient completed trial therapy and pregnancy was detected during trial follow-up period.

[b]Patient developed severe preeclampsia and underwent induction of labor with spontaneous vaginal delivery at 34 weeks and 3 days.

Abbreviation: NA, not applicable.

autoimmune hepatitis, suggesting a difference in the degree of immune modulation at the maternal-fetal interface compared with the tumor or liver [7]. The risk may also be patient-specific despite receiving the same dose of ICI because of differences in the interaction between the allogeneic fetus and the maternal immune system [4].

In our cohort of patients who conceived while on trial, treatment was stopped immediately after pregnancy was discovered. However, it is known from pharmacodynamic assessments that the exposure to immunotherapeutic agents is prolonged because of long half-lives and receptor occupancy after the last administered dose [8, 9]. For example, a single infusion of the PD-1 inhibitor nivolumab demonstrated a mean plateau PD-1 receptor occupancy of 72% at 57 days or greater [8]. In- vitro data from that study suggest that at very low serum levels (below the threshold of detection), there is still sufficient concentration to maintain PD-1 receptor occupancy on T cells.

There are similarities between tumor cells and the developing placenta in their ability to grow within their host while escaping immune surveillance despite both being genetically distinct from the host [7]. PD-L1 is abundantly expressed by the syncytiotrophoblast and extravillous cytotrophoblasts, which are in close contact with maternal blood and tissue, and is positioned to protect the fetus from activated maternal T cells [10]. In murine models, the blockade of PD-L1 signal during pregnancy was shown to cause an almost five-fold increase in spontaneous fetal loss rates in allogeneic pregnancies by expanding alloreactive T-helper cells. Furthermore, female mice deficient in PD-L1 showed an increased rate of allogeneic fetal loss compared with controls [10]. The PD-1 inhibitor nivolumab was tested for prenatal and postnatal development in cynomolgus monkeys from the onset of organogenesis through delivery at doses several-fold higher than the standard treatment dose. This resulted in a non–dose-related increase in spontaneous abortions and neonatal death. However, surviving infants did not have any apparent malformations or other developmental abnormalities through the 6-month postnatal observation period [4].

In the general population, preeclampsia complicates approximately 3% of pregnancies and can be associated with preexisting medical conditions such as hypertension, diabetes mellitus, and antiphospholipid syndrome [11]. It has been suggested that altered PD-1/PD-L1 pathway may contribute to Treg/T-helper 17 (Th17) imbalance in preeclampsia, and therefore, blocking this pathway may induce a propensity to Th17 over Treg immunity at the maternal-fetal interface, leading to the development of preeclampsia [12, 13]. Only one out of the seven women in our study cohort developed preeclampsia. However, the data should be carefully interpreted in the context of causation or association with immunotherapy administration, as the sample size is extremely small and other risk factors for preeclampsia could not be properly assessed.

Conclusion

As the number of patients with cancer receiving immunotherapies continues to grow, with an increasing number of indications for these agents, the issue of pregnancy and conception during treatment with these agents will continue to gain importance. Our study generates limited but important data in patients exposed to immunotherapy agents at the crucial time of conception and organogenesis during the first trimester.

Overall, our data suggest a need for further research in this area to individualize and help generate evidence-based recommendations for contraception during immunotherapy treatment for cancer. Such efforts will allow women with cancer to make informed decisions if they become or wish to become pregnant while on therapy, or if they develop cancer while pregnant.

Disclosures

The authors indicated no financial relationships.

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